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Original Article

The Effect of Hydrocortisone Treatment After Day Fourteen of Life on Preventing Bronchopulmonary Dysplasia in Preterm Infants

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ABSTRACT

Background: This study aimed to evaluate whether administering low-dose hydrocortisone after the first fourteen days of life affects the incidence of bronchopulmonary dysplasia (BPD), mortality, and other short-term complications in mechanically ventilated preterm infants.

Methods: A randomized clinical trial was conducted between 2019 and 2022 in the NICUs of Shariati and Valiasr hospitals in Tehran. Infants received either hydrocortisone or placebo for 10 days and were followed until a corrected gestational age of 36 weeks. Baseline characteristics, primary outcomes, and secondary outcomes were recorded for all participants.

Results: The mean gestational age of infants in this study was 28.2 ± 1.79 weeks. The cohort included 45 male infants (64.3%) and 25 female infants (35.7%). Mortality rates and the need for supportive oxygen treatment were significantly different between the two groups ($P < 0.05$). The rate of hypertrophic myocarditis also differed significantly ($P < 0.05$).

Conclusion: In summary, systemic corticosteroid use led to reductions in mortality and BPD by corrected age of 36 weeks. Although there are differences between dexamethasone and hydrocortisone, hydrocortisone decreased mortality but did not significantly reduce BPD incidence. Moreover, late systemic hydrocortisone treatment significantly shortened the duration of mechanical ventilation in infants.

Keywords: Bronchopulmonary dysplasia, Hydrocortisone, Preterm infants

Introduction

Preterm birth (PB) occurs when an infant is born before 37 completed weeks of gestation. In 2010, approximately 15 million preterm infants were born worldwide, comprising 10% of all live births. PB is a major cause of infant mortality, accounting for an estimated 35% of infant deaths annually (1). While the exact etiology remains unclear, known risk factors include a previous history of preterm delivery and cervical insufficiency (2).

One common complication associated with PB is neonatal respiratory distress syndrome (NRDS), which results from inadequate lung development and surfactant deficiency (3). Insufficient surfactant increases the risk of pneumothorax and respiratory failure, especially in infants under 30 weeks gestation (4). Standard NRDS treatment includes surfactant replacement and respiratory support via mechanical ventilation or CPAP, which reduces mortality in affected preterm infants (5).

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However, long-term respiratory treatment often leads to bronchopulmonary dysplasia (BPD), contributing to morbidity and mortality (6).

BPD—an increasingly prevalent comorbidity in preterm infants—is defined by the need for supplemental oxygen at a corrected gestational age of 36 weeks (7). Infants diagnosed with BPD face higher risks of mortality and impaired future respiratory function. Etiologic factors are broadly categorized into prenatal inflammation (e.g., maternal chorioamnionitis) and postnatal inflammation (e.g., prolonged mechanical ventilation), both of which can damage developing lungs.

Because BPD is driven by inflammatory processes, systemic corticosteroids have been explored as preventive treatments. Dexamethasone and hydrocortisone have both been studied. Dexamethasone is effective in reducing BPD risk and mortality but is associated with severe complications—including intraventricular hemorrhage, gastrointestinal bleeding, sepsis, and long-term neurodevelopmental issues like cerebral palsy. Hydrocortisone, with more limited investigation, has shown reductions in BPD incidence, mortality, and extubation failure, without clear reports of significant adverse effects (8–11).

Despite advances such as prenatal corticosteroids and exogenous surfactant, no definitive treatments reliably prevent BPD. Non-invasive respiratory support has not significantly reduced BPD rates (13). BPD may arise from immune dysregulation associated with prematurity, including prenatal corticosteroids, intrauterine infection, or postnatal sepsis (14). Due to limited evidence regarding low-dose hydrocortisone after the first week of life, this study aims to examine its effects on BPD incidence, mortality, and short-term complications in preterm infants mechanically ventilated during their first 14 days.

Methods

This study was a randomized clinical trial conducted from 2019 to 2022 in the Neonatal Intensive Care Unit (NICU) departments of Shariati and Valiasr hospitals in Tehran. The sample size was determined based on a study by Renault et al. in 2016. The incidence of Bronchopulmonary Dysplasia (BPD) was reported as 30% in the intervention group (hydrocortisone) and 71% in the placebo group (15). With $p = 0.71$, $q = 0.3$, alpha = 0.05, and beta = 0.2, and accounting for a 15% loss to follow-up, the required sample size for each group was calculated to be 35 participants, totaling 70 participants. The inclusion criteria included a gestational age of at least 32 weeks, a birth weight of at least 1500 grams, and the infant's dependence on mechanical ventilation until the 14th day after birth. Exclusion criteria included chromosomal disorders, major congenital malformations, and hereditary metabolic disorders.

Data Collection: Infants were initially treated with either hydrocortisone or a placebo for 10 days and then followed up to a corrected gestational age of 36 weeks. Information related to background variables, as well as primary and secondary outcomes, was recorded for all patients.

Infants enrolled in the study based on the inclusion criteria were randomly assigned to one of the two groups: the intervention (hydrocortisone) group or the control (placebo) group, using a four-block randomization method with two alleles.

Patients in the intervention group received intravenous hydrocortisone according to the following schedule:

- 4 mg/kg per day, divided every 6 hours, for 3 days
- 2 mg/kg per day, divided every 6 hours, for 2 days
- 1 mg/kg per day, divided every 12 hours, for 3 days
- 0.5 mg/kg per day, administered daily, for 2 days

It should be noted that the hydrocortisone dosage was calculated based on the DART study, ensuring equivalence with the recommended dose of dexamethasone. Infants in the control group did not receive corticosteroids.

Before the intervention, background variables were recorded. These included gestational age (weeks), birth weight (grams), gender, type of delivery, maternal chorioamnionitis, prenatal steroid treatment, and low 5-minute Apgar score (less than 3). Primary outcomes collected were the neonatal incidence of bronchopulmonary dysplasia (BPD), mortality, and the combined outcome of BPD and/or mortality. Secondary outcomes included the duration of mechanical ventilation, duration of oxygen support therapy, number of extubation failures, length of hospital stay, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), sepsis, hyperglycemia, hypertension

(HTN), hypertrophic cardiomyopathy (HCM), and gastrointestinal bleeding (GIB).

The duration of the need for oxygen support was defined as the number of days oxygen was required to maintain arterial oxygen saturation above 92%. In this study, bronchopulmonary dysplasia was defined as the need for supplemental oxygen at a corrected gestational age of 36 weeks. Mortality was also assessed up to the corrected gestational age of 36 weeks. Necrotizing enterocolitis was considered positive if it presented with a Bell stage of 2 or higher. Retinopathy of prematurity was considered positive only in cases requiring therapeutic intervention. Intra-ventricular hemorrhage (IVH) was considered positive only in cases of grade 3 and 4. For sepsis to be considered positive, a positive culture from the newborn was required. Hyperglycemia and hypertension were considered positive only in cases requiring drug treatment. Extubation failure was defined as the need for re-intubation within 48 hours after extubation.

The randomization process involved assigning samples to two alleles using random blocks of size 4, resulting in sequences such as: BABABABA, BABA-BBAABBAABBAA, BAABBAAB, BAAB-ABBA, ABBAABBA-ABBAABBAABBAABBA-AABB, AABBAABB.

The placebo and hydrocortisone were identical in appearance and method of administration. The nursing staff and the neonates were unaware of the group assignments, ensuring that the study was double-blinded.

Data Analysis

Following data collection, all information was described using mean and standard deviation for quantitative data, and frequency and percentage for qualitative variables. Chi-Square and Mann-Whitney U tests were used for data analysis. Based on the Kolmogorov-Smirnov test, all quantitative variables in both the control and hydrocortisone groups exhibited a non-normal distribution (p-value < 0.05). Consequently, the non-parametric Mann-Whitney U test was employed for their comparison. Qualitative variables were compared using Fisher's exact test.

Logistic regression was attempted; however, due to the small sample size, a robust model could not be established.

All analyses were performed using SPSS version 26 software, with a significance level set at $P < 0.05$. The power of the study was 80%.

Ethical approval

The study received ethical approval from Tehran University of Medical Sciences, with the ethical approval code: IR.TUMS.IKHC.REC. 1400.411. Following coordination with department officials, informed consent was

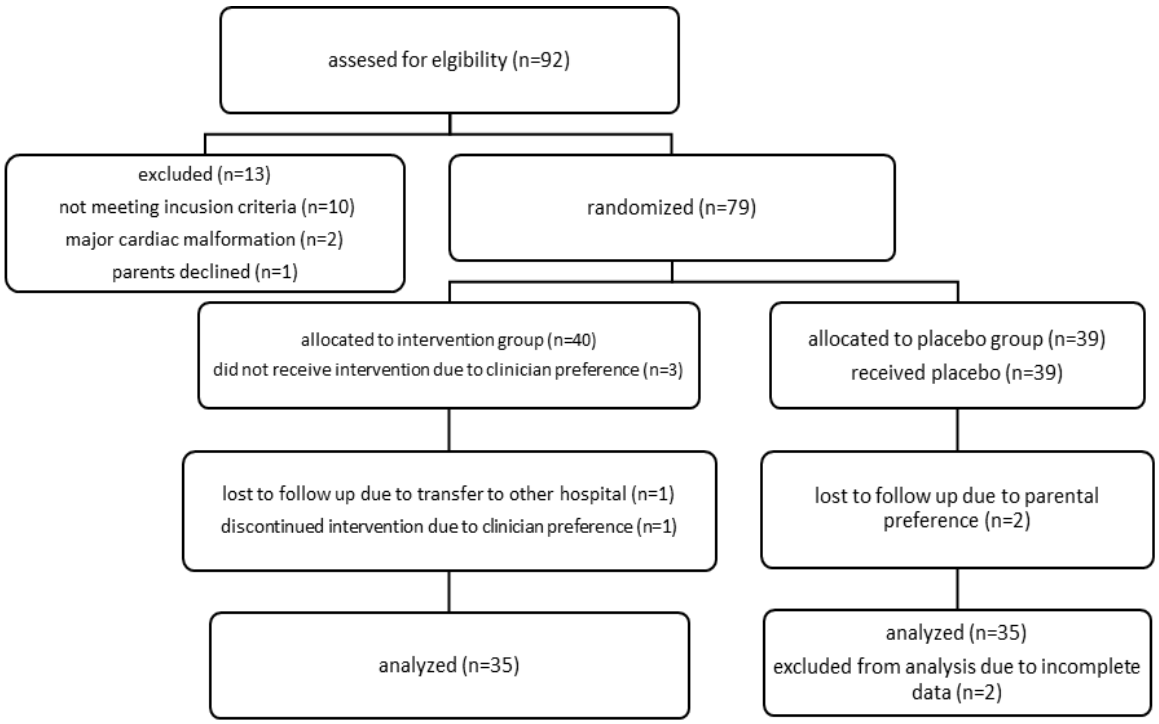

Figure 1. trial flow diagram

obtained from the parents of the participants. All patient information was kept confidential, and only the results were published without mentioning names or personal characteristics. No additional costs were incurred by the patients, and the infants did not forgo any necessary or vital medical measures during their treatment.

Results

This study included 70 preterm infants, who were randomly assigned to one of two treatment groups: hydrocortisone (n=35) or placebo (n=35). The mean gestational age of the infants in this study was 28.2 ± 1.79 weeks. In terms of gender, 45 male infants (64.3%) and 25 female infants (35.7%) participated. Other background and demographic variables are presented in Table 1.

In the subsequent analysis, primary outcomes and background information of the patients were compared between the two groups. The results of this comparison are detailed in Table 2. According to the findings, there was a significant difference in the mortality rate and supportive oxygen treatment between the two groups ($P < 0.05$). No significant differences were observed for other variables between the groups ($P > 0.05$).

Using Fisher's exact test, no significant difference was found in the incidence of BPD between the two groups ($P > 0.05$).

Furthermore, the secondary outcomes of the patients were investigated and measured between the two groups, aligning with the study's objectives. These results are reported in Table 3. Based on the findings, the rate of Hypertrophic Myocarditis showed a significant difference between the two groups ($P < 0.05$). Other variables did not show significant differences between the groups ($P > 0.05$). The results obtained using Fisher's exact test were similar.

Table 1. Background information of patients

Variables	Total (n=70)		Control (n=35)		Hydrocortisone (n=35)		P-value
	Mean/ Frequency	SD/ %	Mean / Frequency	SD/ %	Mean / Frequency	SD/ %	
Gestational age	28.2	1.79	27.85		28.42		0.153
Birth Weight (gr)	1120	425	1080		1060		0.517
Labour type							
Natural childbirth	21	30	14	40	7	20	0.117
Cesarean section	49	7	21	60	28	80	
Maternal chorioamnionitis	9	12.9	5	14.3	4	11.4	0.721
Prenatal corticosteroid administration	35	50	19	54.3	16	45.7	0.633
Five-Minute Apgar							
<3	27	38.6	13	37.1	14	40	0.806
≥3	43	61.4	22	62.9	16	60	

Table 2. primary outcomes

Variables	Total (n=70)		Control (n=35)		Hydrocortisone (n=35)		P-value
	Mean/ Frequency	SD/ %	Mean / Frequency	SD/ %	Mean / Frequency	SD/ %	
BPD	61	87.1	31	88.6	30	85.7	0.128
Mortality	11	15.7	11	31.4	0	0	<0.001
Ventilator treatment (Days)	23.69	9.46	26.66	10.66	20.7	7.05	0.021
Supportive oxygen treatment (Days)	63.3	24.00	62.6	27.8	64.0	19.80	0.906
Extubation Failure							
Once failed	30	42.9					
Twice failed	19	27.1	1.26	0.741	1.54	1.06	0.221
Three times failed	10	14.3					
Admission time (Days)	64.2	24.1	60.4	27.5	67.97	19.85	0.476

Table 3. Investigation and comparison of secondary outcomes in two control and hydrocortisone groups

Variables	Total (n=70)		Control (n=35)		Hydrocortisone (n=35)		P-value
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	
NEC	5	7	3	8.6	2	5.7	1.000
ROP	29	41	17	48.6	12	34.3	0.332
IVH	14	20	7	20.0	7	20.0	1.000
PDA	37	53	20	57.1	17	48.6	0.473
Sepsis	28	40	16	45.7	12	34.3	0.952
Hyperglycemia	5	7	2	5.7	3	8.6	0.215
Hypertension	12	17	2	5.7	10	28.6	0.011
Hypertrophic Myocarditis	14	20	1	2.9	13	37.1	<0.001
GI Bleeding	5	7	3	8.6	2	5.7	0.643

Discussion

This study aimed to investigate the relationship between low-dose hydrocortisone administration and the incidence of BPD, mortality, and other potential short-term complications in premature infants (PIs) who required mechanical ventilation during their first 14 days of life. The mean gestational age of the infants in this study was 28.2 ± 1.79 weeks, with 45 male infants (64.3%) and 25 female infants (35.7%) participating. Our results indicated a significant difference in mortality rate and supportive oxygen treatment between the hydrocortisone and placebo groups ($P < 0.05$). Additionally, the rate of Hypertrophic Myocarditis differed significantly between the two groups ($P < 0.05$).

Further analysis of background variables revealed that 21 infants (30%) were born via natural delivery and 49 infants (70%) via Cesarean section. Clinical chorioamnionitis was present in 12.9% of cases (9 mothers), and prenatal corticosteroids were administered to 50% of the mothers. Furthermore, 27 infants (38.6%) had an Apgar score below 3. The analysis of these background variables did not show any significant differences between the placebo and hydrocortisone groups. We also evaluated the relationship of each of these variables with the primary outcomes (BPD and mortality) using logistic regression. None of the background variables significantly altered the risk of BPD in the infants included in the study.

Bronchopulmonary dysplasia (BPD) was defined as the need for oxygen support to maintain arterial oxygen saturation above 92% at a corrected gestational age of 36 weeks. Numerous studies have explored the risk factors for BPD. Known risk factors identified in previous research include low birth weight, low gestational age, male gender, intrauterine growth restriction, and lung damage from prolonged mechanical ventilation (16, 17-24). Given that many of these studies are cohort-based with large sample sizes, the relatively smaller sample size and the randomized controlled trial (RCT) methodology used in the present study may explain the lack of significant relationships observed between background variables and primary outcomes. It is important to note that assessing BPD risk factors was not a primary objective of this research.

The primary outcomes investigated in this study were the incidence of BPD at 36 weeks corrected gestational age, mortality at 36 weeks corrected gestational age, and the combined outcome of BPD and/or mortality. Our findings indicated an overall incidence of BPD of 87.1% (61 infants), a mortality rate of 15.7% (11 infants), and a combined BPD and/or mortality outcome of 90% (63 infants). Specifically, the incidence of BPD in the placebo group was 88.6% (31 infants), while in the hydrocortisone group, it was 85.7% (30 infants). No significant difference was observed in the incidence of BPD between the placebo and hydrocortisone groups ($P = 0.721$). The mortality rate in the placebo group was 31.4% (11 infants), whereas no mortality occurred in the hydrocortisone group. Statistical analysis confirmed a significant difference in mortality between the control and intervention groups (p-value < 0.001). The incidence rate of the combined outcome of BPD and/or mortality in the control group was 94.3% (33 infants), compared to 85.7% (30 infants) in the intervention group. Statistical analysis did not reveal a significant difference in this combined outcome between the two groups ($P = 0.428$).

A meta-analysis by Doyle et al. (2021), which reviewed 23 clinical trials involving 1817 infants, suggested that late treatment (after the first week of birth) with systemic corticosteroids (dexamethasone or hydrocortisone) significantly reduces both BPD incidence and mortality. However, when studies were separated by

corticosteroid type, mortality was not significantly associated with any specific corticosteroid, and only dexamethasone was found to reduce the risk of BPD, with hydrocortisone showing no significant effect (25). Zhou et al. (2021) reported that low-dose systemic hydrocortisone treatment significantly reduced the risk of mortality and BPD in preterm infants with a history of chorioamnionitis, an effect not observed in infants without this history (26). Watterberg et al. (2022), in a study of 800 infants, evaluated the effect of late treatment (after 14 days) with systemic hydrocortisone on BPD and mortality, concluding no significant difference compared to placebo in survival without moderate to severe BPD (27). Tolia et al. (2019) examined 1427 preterm infants receiving hydrocortisone within 14 days of birth and found that high-dose hydrocortisone was associated with a significantly higher mortality rate compared to low-dose hydrocortisone (28). Holliday et al. (2010) found that early hydrocortisone treatment (within the first 7 days) had no effect on mortality or BPD and only slightly increased the risk of intestinal perforation while decreasing the risk of patent ductus arteriosus (29). A meta-analysis (2010) of 8 clinical trials with 880 infants using early-onset systemic hydrocortisone (within the first week) found no significant relationship with BPD, mortality, or their combined risk, with the only significant association being an increased risk of intestinal perforation (30). Ramaswamy et al. (2021) systematically reviewed evidence suggesting that systemic corticosteroid regimens, including early hydrocortisone, early inhaled fluticasone, late or early high-dose dexamethasone, and intratracheal budesonide, are significantly associated with a reduced risk of BPD or mortality at 36 weeks corrected gestational age (31).

In summary, most studies examining the effect of systemic hydrocortisone on mortality and BPD in preterm infants have found an insignificant relationship between hydrocortisone treatment and BPD, consistent with our findings. However, our study observed a significant reduction in the risk of mortality until 36 weeks corrected gestational age with systemic hydrocortisone treatment. The results regarding hydrocortisone's effect on mortality vary across studies. These discrepancies may be attributed to differences in study methodologies, including the dose used, the timing of intervention, and the specific primary outcomes assessed, particularly mortality. Generally, it appears that low-dose, late-stage systemic hydrocortisone treatment may reduce mortality in preterm infants, but its effect on reducing BPD remains unclear.

Secondary outcomes, including duration of mechanical ventilation, oxygen support therapy, extubation failures, hospitalization duration, and the incidence of NEC, ROP, IVH, PDA, sepsis, hyperglycemia, hypertension, hypertrophic cardiomyopathy, and gastrointestinal bleeding, were also evaluated. Several studies have investigated the relationship between systemic corticosteroid treatment and these variables. Tao et al. (2022) found that the incidence of ROP requiring treatment was significantly associated with lower gestational age, longer mechanical ventilation duration, and higher doses of systemic corticosteroids (32). Kidman et al. (2021) showed that extubation failure rate was significantly associated with BPD, postnatal systemic corticosteroid treatment, duration of mechanical ventilation, noninvasive respiratory support, oxygen therapy, and length of hospital stay (33). Holliday et al. (2001) reported that infants treated with early dexamethasone had a lower risk of PDA and more hyperglycemia compared to those receiving late dexamethasone. Dexamethasone, whether early or late, was associated with a significant increase in the risk of hypertension and gastrointestinal problems (34).

Holliday et al. (2010) concluded in a meta-analysis that systemic corticosteroid treatment within the first 7 days after birth in preterm infants could positively impact earlier extubation, reduce the risk of chronic lung disease at 28 days, facilitate extubation at 36 weeks corrected gestational age, and lead to less open ductus arteriosus and a lower incidence of retinopathy of prematurity, especially severe forms. However, there was no significant association between early corticosteroid treatment and neonatal mortality, infection (sepsis), severe IVH, periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), or pulmonary hemorrhage. The risks of gastrointestinal bleeding, intestinal perforation, hyperglycemia, hypertension, hypertrophic cardiomyopathy, and growth failure increased with early corticosteroid therapy. Dexamethasone demonstrated more beneficial effects alongside more side effects, whereas hydrocortisone had minimal effects on patient outcomes, with only a slight increase in the risk of intestinal perforation and a decrease in the risk of patent ductus arteriosus (34).

A meta-analysis investigating systemic corticosteroid treatment between 7-14 days postpartum in preterm infants indicated that

relatively early treatment significantly reduces 28-day mortality and the incidence of chronic lung disease, and is associated with earlier extubation. No significant relationship was found between this treatment and pneumothorax, severe retinopathy of prematurity (severe ROP), or necrotizing enterocolitis (NEC). Side effects significantly associated with early treatment included hyperglycemia, hypertension, hypertrophic cardiomyopathy, and infection (sepsis) (35). Tsukahara's study found that early dexamethasone treatment was significantly associated with reduced duration of mechanical ventilation and extubation failure, but this association was not significant for complications like infection, PVL, or ROP (36). Doyle et al. (2017) found that late treatment with systemic corticosteroids was significantly related to reduced extubation failure and duration of home oxygen support. Conversely, late treatment increased the risk of infection, gastrointestinal bleeding, hyperglycemia, hypertension, glycosuria, severe ROP, and IVH in preterm infants, but did not increase the risk of NEC (25). A 2010 meta-analysis on the effect of premature systemic hydrocortisone in preterm infants found that early treatment had no significant relationship with reduced BPD or mortality and was not associated with specific complications other than intestinal perforation (30). Haroon et al. (2001) found postnatal dexamethasone treatment to be significantly associated with the incidence of severe ROP (37). Morales et al. (1998) reported that early dexamethasone treatment significantly reduced the duration of mechanical ventilation and the incidence of PDA in preterm infants (38). Ramaswamy et al. noted that systemic and inhaled corticosteroid regimens reduced extubation failure rates. Early systemic hydrocortisone was associated with a higher risk of intestinal perforation compared to other regimens, while late dexamethasone was associated with higher risks of hypertension and hypertrophic cardiomyopathy (31). Termato et al. found that postnatal systemic hydrocortisone treatment did not increase the incidence of ROP or severe ROP, with only a very small amount of hydrocortisone increasing the risk of severe ROP in infants already diagnosed with ROP (39).

This study has limitations, including a small sample size and the inherent instability of preterm neonates in their early days, which often necessitates varied treatment plans that could impact outcomes and were not fully accounted for in this study.

Conclusion

Both early and late systemic corticosteroid treatment, encompassing dexamethasone and hydrocortisone, demonstrates a reduction in mortality and bronchopulmonary dysplasia (BPD) rates by 36 weeks corrected gestational age, albeit with noted differences between the agents. Hydrocortisone appears to decrease mortality without significantly impacting BPD incidence. Furthermore, late-stage systemic hydrocortisone treatment has been shown to significantly shorten the duration of mechanical ventilation in infants. However, the side effects associated with late hydrocortisone treatment are varied across studies. Within the scope of the present study, late, low-dose hydrocortisone treatment was found to significantly increase the risk of hypertrophic cardiomyopathy and hypertension.

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Conflicts of interest

The authors declare no conflict of interest.

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